Br Heart J 1980; **44**: 309–16

Left ventricular function in Friedreich's ataxia*
An echocardiographic study

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SUMMARY Left ventricular function was assessed in seven patients with Friedreich's ataxia using computer-assisted analysis of the left ventricular echocardiograms and compared with those of 45 normal children matched for age and sex. The left ventricle in Friedreich's ataxia was symmetrically hypertrophied, cavity dimension was normal or small, and septal motion and peak velocity of circumferential shortening were normal in all patients. In diastole the duration of rapid filling was normal, peak rate of increase in left ventricular dimension was reduced in two patients, mitral valve opening was delayed with respect to minimum cavity dimension in seven, and there were significantly greater than normal increases in left ventricular dimension during the isovolumic period to mitral valve opening in seven, indicating abnormal and incoordinate relaxation. Peak rates of posterior wall systolic thickening and diastolic thinning were reduced in four and six patients, respectively, whereas peak rates of septal systolic thickening and diastolic thinning were reduced in one and four, respectively, suggesting a disproportionately greater impairment of the posterior wall than of septal function.

The absence of asymmetric septal hypertrophy and mid-systolic closure of the aortic valve, the presence of normal septal motion, and the greater reduction in posterior wall than in septal dynamics are inconsistent with previous ideas that the heart disease of Friedreich's ataxia is identical to hypertrophic cardiomyopathy.

Computer-assisted analysis of echocardiograms permits recognition of heart disease in Friedreich's ataxia before the onset of cardiac symptoms or development of clinical signs of heart disease.

Friedreich's ataxia is a rare spinocerebellar neuromyelopathy, usually transmitted as an autosomal recessive.[1] It is characterised by the early onset of progressive ataxia, dysarthria, posterior column signs in the lower limbs, and muscle weakness.[2 3] Though myocardial involvement in Friedreich's ataxia is well documented and many patients die from heart failure,[4 5] cardiovascular symptoms and signs usually develop late in the course of the disease.[6] Clinical examination is complicated because (1) auscultatory abnormalities occur only in a minority[6–8]; (2) radiographic evidence of cardiomegaly is uncommon[8] and may be difficult to assess in the presence of coexistent scoliosis[2]; and (3) a wide range of non-specific electrocardiographic abnormalities occurs.[9]

Previous echocardiographic studies have shown no constant abnormality. Thus left ventricular dimension can be normal or small, left ventricular hypertrophy concentric or asymmetric, and systolic anterior movement of the mitral valve may or may not be present. Haemodynamic and angiographic studies have shown similar variability in left ventricular function with and without left ventricular outflow tract obstruction.[10–13] Since there appear to be no specific diagnostic features by which cardiac involvement in Friedreich's ataxia may be recognised, we used computer-assisted analysis of left ventricular echocardiograms in an attempt to determine whether any abnormalities of regional

* This investigation was supported in part by Research grants from the National Institute of Health, Public Health Service, and from the National Aeronautics and Space Administration.

Received for publication 24 September 1979

or cavity function were consistently present, which might enable earlier recognition of cardiac disease, and possibly prove useful in the reassessment of patients at periodic follow-up.

Subjects

NORMALS

Left ventricular echocardiograms were recorded in 45 clinically normal schoolchildren (24 girls and 21 boys) aged from 9 to 15 years (mean age 12 years) in order to obtain normal values for septal, posterior wall, and left ventricular internal dimensions in subjects of this age. Fifteen of these echocardiograms (eight female and seven male) were digitised to provide normal data for septal, posterior wall, and left ventricular cavity dynamics which were used as a basis for comparison with that recorded from the children with Friedreich's ataxia.

PATIENTS WITH FRIEDREICH'S ATAXIA

Left ventricular echocardiograms were recorded from seven children (three girls and four boys) aged from 9 to 15 years (mean age 12 years) (Fig. 1). The diagnosis of Friedreich's ataxia was established clinically and supported by electromyography in all seven patients who were referred for cardiac assessment by the division of neurology at the Mayo Clinic where they all attended for regular follow-up. Two of the patients were sibs and one other patient had a sib with Friedreich's ataxia, but the latter was not available for echocardiographic examination. All patients were in sinus rhythm at the time of examination, and none was taking any drugs known to affect myocardial performance.

Methods

ECHOCARDIOGRAPHIC RECORDINGS

Echocardiograms were obtained with an Ekoline 20 Ultrasonoscope using a 2·25 MHz transducer with a repetition frequency of 1000 cycles/s. Recordings were made on a Cambridge Scientific Instruments multichannel strip-chart recorder at paper speeds of 50 to 100 mm/s, with simultaneous electrocardiograms. Echoes of the right and left sides of the septum and the endocardium and epicardium of the posterior left ventricular wall were obtained at the level of the mitral valve. Echocardiograms were only accepted for analysis when these echoes were clear and continuous throughout the cardiac cycle. Echocardiograms were digitised[14] using a Science Accessories Corporation Graf pen and processed by a Control Data 3500 computing system. Data points were generated for both right and left sides of the septum, and the endocardial and epicardial surfaces of the posterior left ventricular wall, so that strings of XY co-ordinates were obtained for the four surface boundaries. The echoes were calibrated with points defining a time interval of 2000 ms, a depth of 4 cm, and two

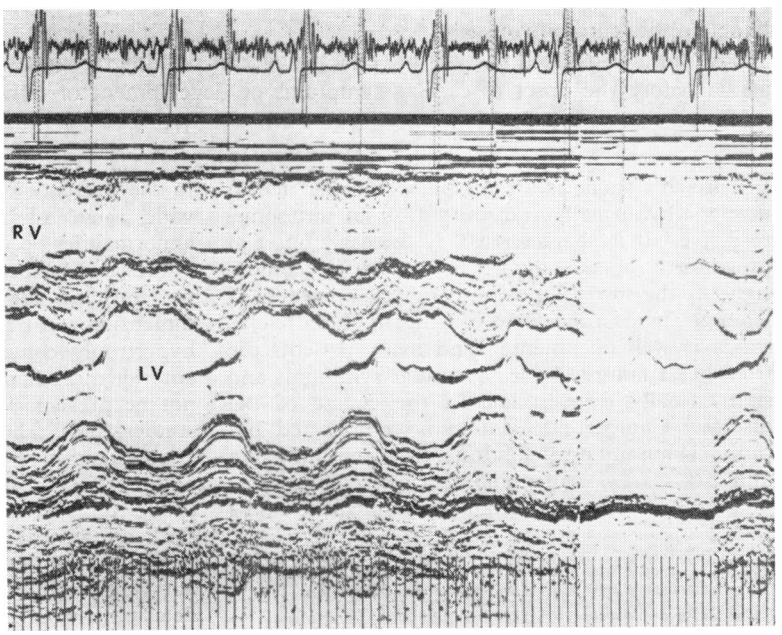

Fig. 1 *Echocardiogram of patient with Friedreich's ataxia showing right ventricle, interventricular septum, left ventricular cavity, and posterior wall, with electrocardiogram and phonocardiogram at top.*

successive Q waves on the electrocardiogram enclosing the cardiac cycle to be analysed. Plots were made of continuous left ventricular cavity, septal, and posterior wall dimensions, and their rates of change expressed either in cm/s, or normalised to refer to unit cavity dimension, or septal and posterior wall thickness. From these plots (Fig. 2 and 3) the following measurements were made.

(1) *Dimensions*

(a) Maximum and minimum left ventricular cavity dimensions.

(b) Percentage left ventricular cavity shortening.

(c) Maximum and minimum posterior wall thicknesses.

(d) Maximum and minimum septal thicknesses.

(e) Ratio of minimum septal to minimum posterior wall thicknesses.

(2) *Systolic left ventricular function*

Normalised velocities:

(a) Normalised peak rates of left ventricular cavity dimension change.

(b) Normalised peak rates of posterior wall thickening.

(c) Normalised peak rates of septal thickening.

(3) *Diastolic left ventricular function*

Time intervals:

(a) Time from minimum left ventricular cavity dimension (when the first derivative of cavity dimension changed from negative to positive) to the onset of mitral valve opening, defined as the initial separation of the mitral valve cusps.

(b) Time from mitral valve opening to the discontinuity on the plot of continuous left ventricular cavity dimension (taken as the point in time at which the left ventricular rate of

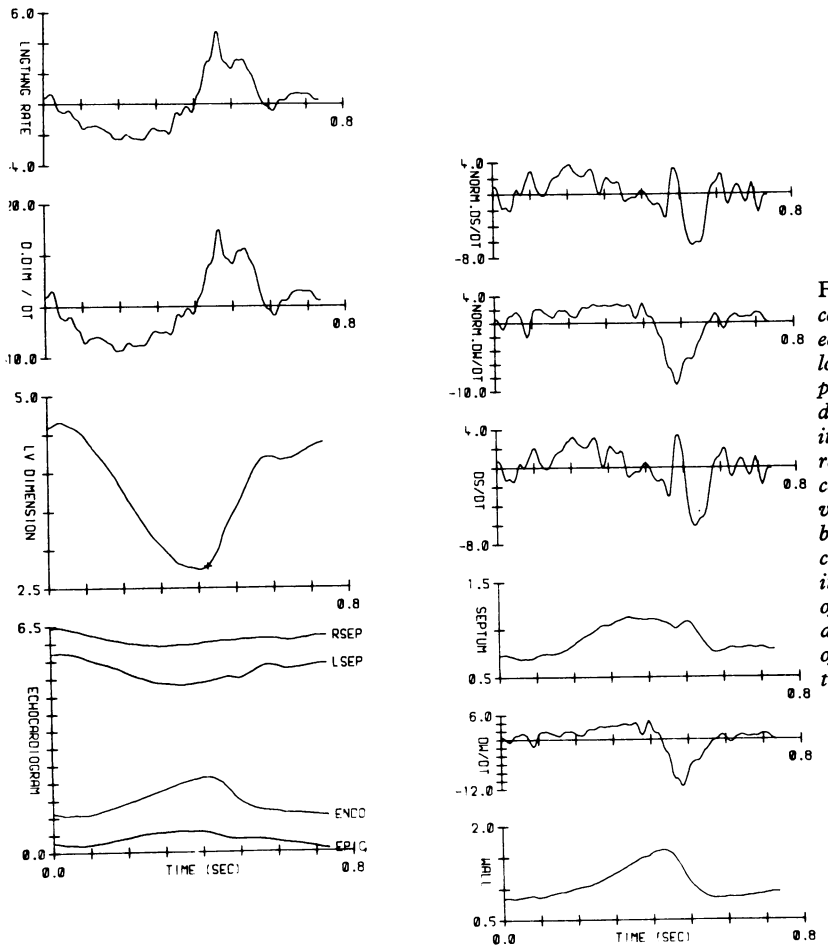

Fig. 2 *Normal child. Set of computer plots from the digitised echocardiogram reproduced in lowest panel on left. Above it are plots of continuous left ventricular dimension, its rate of change and its normalised rate of change, respectively. On the right panel—continuous posterior left ventricular wall dimension at bottom, above its rate of change, continuous septal dimension, and its rate of change, normalised rate of change of wall thickness, and at top normalised rate of change of septal thickness.* (X *denotes timing of mitral valve opening.*)

increase in dimension dropped abruptly to 20 per cent of its peak value) which represents the true rapid filling period.

Change in left ventricular dimension during the following time interval:

Change in left ventricular cavity dimension during the time interval between minimum left ventricular dimension and mitral valve opening expressed as a percentage of the total change in left ventricular dimension occurring from end-systole to end-diastole.

Velocities of dimension change:

(a) Peak rate of increase in left ventricular dimension.
(b) Normalised peak rates of posterior wall thinning.
(c) Normalised peak rates of septal thinning.

Results

DIMENSIONS

The 95 per cent confidence limits for maximum and minimum left ventricular internal dimensions percentage shortening, maximum and minimum septal and posterior wall thicknesses, and the ratio of minimum septal to minimum posterior wall thicknesses are shown for the normal children in Table 1, and represent the mean values plus and minus 2 standard deviations from the mean.

Maximum and minimum internal left ventricular dimensions in the patients with Friedreich's ataxia were significantly reduced in five of seven (<95% confidence limits) and normal in two of seven. However, percentage left ventricular cavity shortening and septal motion were normal in all patients. The septum and posterior wall in all patients with Friedreich's ataxia were hypertrophic in so far as their minimum thicknesses were either at or in excess of the 95 per cent confidence limits for normal children of the same age and sex (Table 1, Fig. 1 and 2). Maximum septal and posterior wall thicknesses were normal in all except two children in whom both were increased, and the ratio of minimum septal to minimum posterior wall thick-

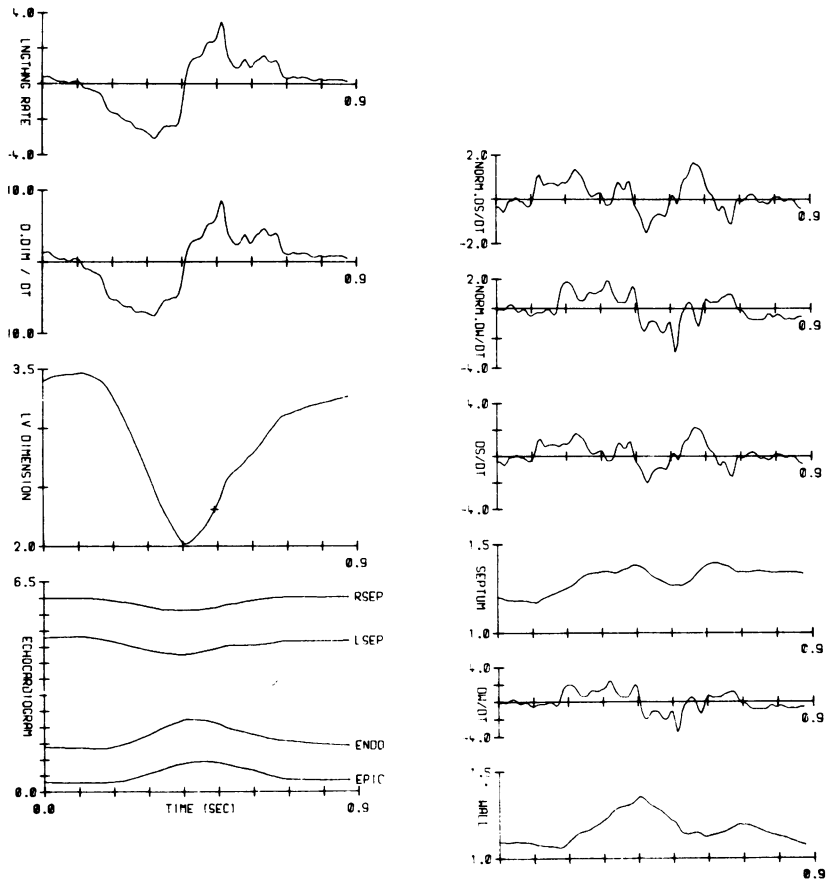

Fig. 3 *Friedreich's ataxia. Set of plots laid out as in Fig. 2. Note reduction in peak rate of increase in left ventricular dimension during diastole, delay in mitral valve opening* (X)*, with respect to minimum dimension and in addition reduced normalised peak rates of septal and posterior wall thickening and thinning.*

Table 1 *Echocardiographic measurements of left ventricular dimensions*

Case no.	*LV cavity dimensions (cm)*		*Per cent cavity shortening*	*Septal dimensions (cm)*		*Posterior LV wall dimension (in.)*		*Ratio of minimum septal to minimum PW thickness*
	Max	*Min*		*Max*	*Min*	*Max*	*Min*	
1	3·7	1·8	51	1·4	1·1	1·9	0·9	1·2
2	3·3	1·6	52	1·4	1·1	1·7	1·1	1·0
3	3·2	1·1	65	1·5	1·2	1·9	1·1	1·1
4	3·2	1·6	50	1·3	0·9	1·5	0·9	1·0
5	2·8	1·6	43	1·2	1·0	1·4	1·0	1·0
6	4·0	2·6	35	1·4	1·1	1·5	1·1	1·0
7	3·5	2·0	43	1·5	1·3	1·4	1·1	1·2
Mean	3·4	1·8	47	1·4	1·1	1·6	1·0	1·1
Normals (n=45)	4·5 ±0·5	2·8 ±0·3	39 ±5	1·1 ±0·2	0·7 ±0·1	1·2 ±0·2	0·7 ±0·1	1·0 ±0·1
Normal range mean ±2S·D	3·7 to 5·3	2·3 to 3·4	29 to 49	0·7 to 1·5	0·5 to 0·9	0·8 to 1·6	0·5 to 0·9	0·8 to 1·2

nesses was 1·1 indicating that the left ventricular hypertrophy was concentric (Table 1).

SYSTOLIC LEFT VENTRICULAR FUNCTION

Normalised peak rates of increase in left ventricular cavity dimension or peak V_{CF} were normal in all patients with Friedreich's ataxia (Table 2, Fig. 3). Normalised peak rates of septal thickening were within normal limits in all except one patient in whom it was reduced, while peak rates of systolic thickening of the posterior wall were significantly reduced in four of seven patients (Table 2), indicating a greater impairment of systolic function of the posterior wall than of the septum.

DIASTOLIC LEFT VENTRICULAR FUNCTION

Time intervals

The time interval from minimum left ventricular cavity dimension to mitral valve opening was significantly prolonged in all patients—the delay varying from 63 to 90 ms longer than in the normal children (Table 2).

The duration of true rapid filling represented by the time from mitral valve opening to the discontinuity on the left ventricular dimension plot, when the rate of change of dimension had fallen to 20 per cent of its peak value, was normal in all patients (Table 2).

Changes in left ventricular dimension before mitral valve opening

Changes in left ventricular cavity dimension during the short time interval between minimum left ventricular dimension and mitral valve opening in the normal children (0 to 15 ms), before the phase of rapid filling, were very small and amounted to no more than 7 per cent of the total increase occurring from end-systole to end-diastole (Table 2, Fig. 2). By contrast in the patients with Friedreich's ataxia, not only was this time interval prolonged,

Table 2 *Echocardiographic assessment of left ventricular function*

Case no.	*Peak V_{CF} 5 to 1*	*MVO (ms)*	*Peak dD/dt (diastolic) (cm/s)*	*Rapid diastolic filling period (ms)*	*Per cent increase in LV dimension from minimum down to MVO*	*Normalised peak rate of systolic thickening of septum and posterior wall*		*Normalised peak rate of diastolic thinning of septum and posterior wall*	
1	3·8	63	11·0	163	17	2·1	3·9	1·9	6·2
2	4·1	81	10·0	127	13	2·7	4·1	1·8	3·4
3	4·3	90	12·0	112	22	2·2	2·1	3·0	4·0
4	3·7	61	9·0	167	16	3·1	4·0	2·8	3·7
5	3·4	73	7·8	215	17	2·2	2·3	2·0	3·9
6	2·4	80	8·2	192	21	2·2	2·0	3·1	2·7
7	2·3	87	6·8	227	14	1·5	2·3	1·2	1·8
Mean	3·4	76	9·3	172	17	2·2	2·9	2·3	3·6
Normals (n=15)	3·1 ±0·5	11 ±6	13·5 ±2·4	176 ±34	0 to 7	3·1 ±0·6	3·8 ±0·7	3·6 ±0·7	6·8 ±1·3
Normal range mean ±2S·D	2·1 to 4·1	0 to 23	8·3 to 18·3	112 to 224	0 to 7	1·9 to 4·3	2·4 to 5·2	2·2 to 5·0	4·2 to 9·4

but there were significantly greater increases in left ventricular dimension of up to 22 per cent (Table 2, Fig. 3).

Velocities of dimension change

Peak rates of increase in left ventricular dimension during diastole were significantly reduced in two patients, at the lower limits of normal in two further children with Friedreich's ataxia, but in the middle of the normal range in three.

Normalised peak rates of septal thinning were significantly reduced in four patients and normal in three, while the peak rates of posterior wall thinning were below the 95 per cent confidence limits in six of seven patients (Table 2). These results indicate that not only is the septal function impaired in fewer patients than the posterior wall, but also that diastolic thinning of the septum and posterior wall is more frequently reduced than their respective peak rates of systolic thickening.

CLINICAL FINDINGS

Six of the seven patients had no symptoms referable to the cardiovascular system, and one had chest pain suggesting angina. On physical examination five patients had grade 2/4 ejection systolic murmurs at the left sternal border, and these were the only abnormal clinical cardiac signs. Three patients had moderate kyphoscoliosis (Table 3).

Chest *x*-ray film showed a normal heart size (cardiothoracic ratio $< 0{\cdot}5$) and normal pulmonary vasculature in all patients. Electrocardiograms showed sinus rhythm in all cases, and the only abnormal findings were non-specific T wave changes in three patients, which were present in the inferior or anterolateral leads. There were no abnormalities of intraventricular conduction and no evidence of left ventricular hypertrophy (Table 3).

The one patient with angina had systolic anterior motion of the mitral valve echocardiographically. At cardiac catheterisation there was no left ventricular outflow tract gradient at rest, but a gradient of 20 to 30 mmHg with isoprenaline.

There was no apparent relation between left ventricular cavity, septal, or posterior wall dynamics, and clinical or electrocardiographic signs; and none of these measurements was of any value in identifying the patient with angina or systolic anterior motion of the mitral valve.

Discussion

The incidence of clinical heart disease in Friedreich's ataxia is well documented, and has been reported to vary from 50 to 90 per cent,[7–9] though abnormal myocardial fibre morphology and extensive interstitial fibrosis were present in 100 per cent of the hearts examined at necropsy.[4 15] Though most patients with Friedreich's ataxia die from heart failure or cardiac arrhythmia rather than from neurological causes,[5] the nature and aetiology of the left ventricular disease remains unresolved. It was initially suggested that the underlying myocardial lesion was hypertrophic cardiomyopathy,[6 16] because asymmetric septal hypertrophy[16] and systolic anterior motion of the mitral valve[5] were described echocardiographically, and because in a few patients left ventricular outflow tract obstruction was documented haemodynamically.[10 12 13 17] Few attempts, however, have been made to assess left ventricular function in Friedreich's ataxia or indeed to identify abnormalities which might enable early recognition of cardiac involvement in this disease, which is somewhat surprising since heart failure accounts for more than 50 per cent of the deaths. Echocardiographic studies are limited in number and have been confined to enumerating qualitatively abnormal features such as asymmetric septal hypertrophy and systolic anterior motion of the mitral valve in spite of the fact that this technique lends itself especially well to repeated left ventricular function studies in children and young adults in whom this disease predominates.[3] Cardiac catheter studies have shown that myocardial dysfunction is

Table 3 *Clinical findings*

Case no.	*Signs*	*Cardiac symptoms*	*Electrocardiogram*	*Chest radiograph*	
				Heart size	*Kyphoscoliosis*
1	Ejection systolic murmur 2/4	None	Inverted T waves II, III, aVF	N	+
2	Ejection systolic murmur 2/4	None	N	N	N
3	Ejection systolic murmur 2/4	Chest pain ? angina	Inverted T waves V4–6	N	N
4	Ejection systolic murmur 2/4	None	N	N	N
5	None	None	N	N	N
6	Ejection systolic murmur 2/4	None	Inverted T waves II, III, aVF	N	+
7	None	None	N	N	+

almost invariable, as indicated by the raised left ventricular end-diastolic pressure and reduced contractility angiographically,[10 12 13 17] and that left ventricular outflow tract obstruction is rare.[10 17]

The present study showed that left ventricular internal dimensions in Friedreich's ataxia are either reduced or normal, and that normal percentage shortening is preserved because of the universal presence of normal septal motion. The reduction in left ventricular cavity size is accounted for by the increased septal and posterior wall thicknesses compared with age- and sex-matched normal subjects, and, in contrast to previous reports,[6 16] the left ventricular hypertrophy was concentric and not asymmetric as shown by the ratio of minimum septal to posterior wall thicknesses, which was close to unity.

Systolic rates of inward wall movement assessed in terms of peak velocity of circumferential fibre shortening, peak V_{CF}, were normal in all patients with Friedreich's ataxia. In spite of this, however, abnormalities of systolic function were detectable in that the peak rates of systolic thickening of the posterior wall were significantly reduced compared with normal in more than half the patients, while septal thickening was only abnormal in one patient. These results suggest that in this disease there is a disproportionately greater impairment of systolic function of the posterior wall than of the septum.

An independent manifestation of left ventricular disease which has been little recognised until recently is diastolic dysfunction, which may even develop before systolic abnormalities occur.[18 19] Diastolic abnormalities, however, other than static pressure-volume characteristics, are less accessible to measurement than systolic or pump function, but are made readily available with computer-assisted analysis of echocardiograms. Using this technique, we found diastolic abnormalities of left ventricular function in all patients with Friedreich's ataxia, and a constant feature was the significant delay in mitral valve opening with respect to minimum left ventricular dimension, events which were synchronous in normal children. The duration of the true rapid diastolic filling period was normal in all patients, though the peak rate of increase in left ventricular dimension during diastole was significantly reduced in two patients to a degree observed in left ventricular inflow tract obstruction caused by moderate mitral stenosis.[14] However, this disturbance of left ventricular filling was not a result of obstruction at mitral valve level since mitral valve echoes were entirely normal and must therefore reflect reduced rates of outward wall movement caused by abnormal left ventricular relaxation. Further evidence of abnormal diastolic function was provided by the significantly greater than normal increases in left ventricular dimension during the isovolumic period between minimum left ventricular dimension and mitral valve opening, which must represent abnormal cavity shape changes resulting from incoordinate relaxation. That myocardial diastolic function in Friedreich's ataxia is abnormal is also corroborated by previous reports of increased left ventricular end-diastolic pressure with normal cavity volume,[10 11 17] indicating increased stiffness and reduced distensibility. In addition, peak rates of septal and posterior wall thinning were significantly reduced in the majority of patients though this reduction occurred more commonly in the posterior wall than in the septum, and these changes were detectable even when the peak rate and duration of cavity filling were normal. These more frequent diastolic abnormalities of cavity, septal, and posterior wall function suggest that relaxation more readily loses its high degree of organisation than does contraction, becoming not only slow but incoordinate, while systolic function may remain normal, or only become abnormal later. This late development of contraction abnormalities may in part explain the delay in appearance of cardiac signs and symptoms in this disease, which moreover vary independently of the severity and rate of progression of the neurological disorder.

The aetiology of the left ventricular dysfunction in Freidreich's ataxia remains unresolved. However, in contrast to previous reports,[6 16] the left ventricle is unlike that in hypertrophic cardiomyopathy in so far as the septum was not hypokinetic, septal motion was normal in all patients, left ventricular hypertrophy was concentric and not asymmetric, systolic anterior motion of the mitral valve was uncommon and mid-systolic aortic valve closure was absent. In addition, reduction in peak rates of systolic thickening and diastolic thinning were both more pronounced in the posterior wall than in the septum which is the reverse of that occurring in hypertrophic cardiomyopathy. Furthermore, histological examination of the hearts in Friedreich's ataxia showed severe interstitial fibrosis which is no more frequent in hypertrophic cardiomyopathy than in normal hearts[20 21] and fibre disarray, which may be regarded as the hallmark of hypertrophic cardiomyopathy[22] was absent.[15]

Left ventricular function in Friedreich's ataxia also differed conspicuously from that in dystrophia myotonica, another neurocardiac disorder, in which there was early and important impairment of systolic function demonstrable as reduced peak V_{CF} and ejection fraction.[23] It also was different from that in Duchenne's muscular dystrophy in which myocardial function is well preserved.[24]

This preponderance of diastolic abnormalities, with maintenance of relatively normal systolic function, also occurs in association with left ventricular hypertrophy secondary to systemic hypertension and aortic stenosis[25] and, therefore, they could theoretically be a manifestation of left ventricular hypertrophy in Friedreich's ataxia. However, it seems more likely that, with the inexorable and rapid deterioration of left ventricular function in Friedreich's ataxia, resulting in death in the second and third decades, it relates more to the replacement of myocardial fibres with non-contractile fibrous tissue—a florid and invariable histological finding—than simply to left ventricular hypertrophy which in any case was not extremely severe.

Patients such as these are not only of theoretical interest because of the appearance of diastolic rather than systolic abnormalities, but they are also of practical diagnostic value in that (1) myocardial involvement in Friedreich's ataxia may be recognised earlier and reassessed at follow-up, and (2) such abnormalities provide early evidence of the clinical syndrome described as heart failure.

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